Send Orders for Reprints to reprints@benthamscience.net

Infectious Disorders - Drug Targets, 2025, *25*, e220724232138

EDITORIAL

Unveiling the Role of SARS-CoV-2 or mRNA Vaccine Spike Protein in Macrophage Activation Syndrome (MAS)

Ziad Fajloun[1,2], Layla Tajer[2], Ziad Abi Khattar[3] and Jean-Marc Sabatier[4,*]

[1]Faculty of Sciences 3, Department of Biology, Lebanese University, Campus Michel Slayman Ras Maska, 1352 Tripoli, Lebanon; [2]Department of Cell Culture, Laboratory of Applied Biotechnology (LBA3B), Azm Center for Research in Biotechnology and its Applications, EDST, Lebanese University, Tripoli P.O. Box 1300, Lebanon; [3]Faculty of Medicine and Medical Sciences, University of Balamand, Kalhat, Tripoli P.O. Box 100, Lebanon; [4]Aix-Marseille Univ, CNRS, INP, Inst Neurophysiopathol, 13385 Marseille, France

ARTICLE HISTORY

Received: July 01, 2024
Accepted: July 12, 2024

DOI:
10.2174/0118715265341206240722050403

1. INTRODUCTION

Macrophage Activation Syndrome (MAS), a severe and life-threatening disorder, is a subtype of secondary hemophagocytic lymphohistiocytosis [1, 2]. MAS is characterized by an excessive and uncontrolled immune response involving the activation and proliferation of macrophages and T lymphocytes, leading to a hyperinflammatory state marked by elevated levels of proinflammatory cytokines known as a "cytokine storm," linked to hemophagocytosis [3]. Macrophages are among the immune system's first responders and play a dual role as effectors and sentinels. They combat pathogens by phagocytosing them and inducing death in infected cells. Macrophages also activate both innate and adaptive immune responses by orchestrating immune responses in specific tissues or throughout the body *via* activating chemokines, cytokines, and growth factors, as well as by presenting antigens to adaptive immune cells [4]. Furthermore, they also play crucial roles in injury repair, tissue rejuvenation, and maintaining homeostasis [5]. MAS is an old syndrome with an incidence estimated at 0.16-0.4/100,000 inhabitants, a prevalence of 1-24/million inhabitants, and the median age at diagnosis varying from 27 to 36 years [6].

Classically activated macrophages are induced by interferon-γ (IFNγ), which is generated during adaptive immune responses by $CD4^+$ or $CD8^+$ T cells, innate immune responses by natural killer (NK) cells, and by tumor necrosis factor (TNF), which is produced by antigen-presenting cells [7]. Hence, MAS can occur spontaneously (primary MAS) or as a secondary complication of microbial infections, rheumatism, tumors, or medications (secondary MAS), with rheumatism (Systemic Juvenile Idiopathic Arthritis (SJIA)) being the most frequent cause of MAS [3, 8, 9]. In the case of arthritis, elevated levels of cytokines, such as IL-1, IL-6, IL-18, and TNFα are produced. On the other hand, in cases of infections (bacterial, parasitic, viral, or fungal), pathogen-associated molecular patterns are sensed by toll-like receptors (TLRs), also leading to the production of inflammatory cytokines. This increased production of proinflammatory mediators (IL-2, IL-6, IL-8, IFNγ, TNFα, GM-CSF, and M-CSF) in both scenarios can amplify TLR signaling. Moreover, infections also stimulate the activation and proliferation of $CD8^+$, $CD4^+$ T cells, and NK cells, resulting in IFNγ secretion. Elevated levels of IL-18 further boost IFNγ production from activated lymphocytes. The resulting IFNγ binds to the IFNγ receptor (IFNGR) and subsequently induces phosphorylation of STAT1 by JAK1 and JAK2 in the cytoplasm. The STAT1 dimer binds to the γ-interferon activation site (GAS) and enhances the transcription of interferon-stimulated genes, such as interferon regulatory factor 1 (IRF1), thereby causing MAS. The activation of STAT1 by IFNγ can also induce micropinocytosis, leading to engulfment and degradation of erythrocytes (Fig. **1**) [10-12].

The symptoms of MAS are often similar and confused with several active autoimmune diseases or sepsis, leading to delayed diagnosis, worsening outcomes, and increased mortality and morbidity [6, 8]. This confusion is exacerbated by the absence of specific diagnostic tests or established criteria for distinguishing MAS from SJIA [10]. Manifestations of this illness typically include persistent high-grade fever, skin rash and hemorrhagic manifestations (such as petechiae, ecchymosis, purpura, bruising, intravascular coagulation, gastrointestinal and mucosal bleeding), hepatosplenomegaly, lymphadenopathy, abnormal liver function, lung failure (including pleural effusion, respiratory failure, pneumonia, interstitial infiltrates, pleurisy, pulmonary hemorrhage, acute respiratory distress syndrome), icterus, renal failure, proteinuria, hematuria, neurological impairment (manifesting as irritability, disorientation, lethargy, headache, seizures, coma, mood swings, confusion) and cardiac failure (pericardial involvement, arrhythmia, heart failure, cardiomegaly) [6, 8, 13, 14]. Laboratory findings of MAS typically show elevated ferritin and aspartate aminotransferase levels, decreased platelet and white blood cell counts (lymphopenia), hypofibrinogenemia, neutropenia, anemia, and low NK cell counts. Additionally, in many cases, checking for bone marrow hemophagocytosis is necessary [8, 13, 15].

*Address corrospondence to this author at the Aix-Marseille Univ, CNRS, INP, Inst Neurophysiopathol, 13385 Marseille, France; E-mail: sabatier.jm1@gmail.com

2212-3989/25 © 2025 Bentham Science Publishers

Infectious Disorders – Drug Targets

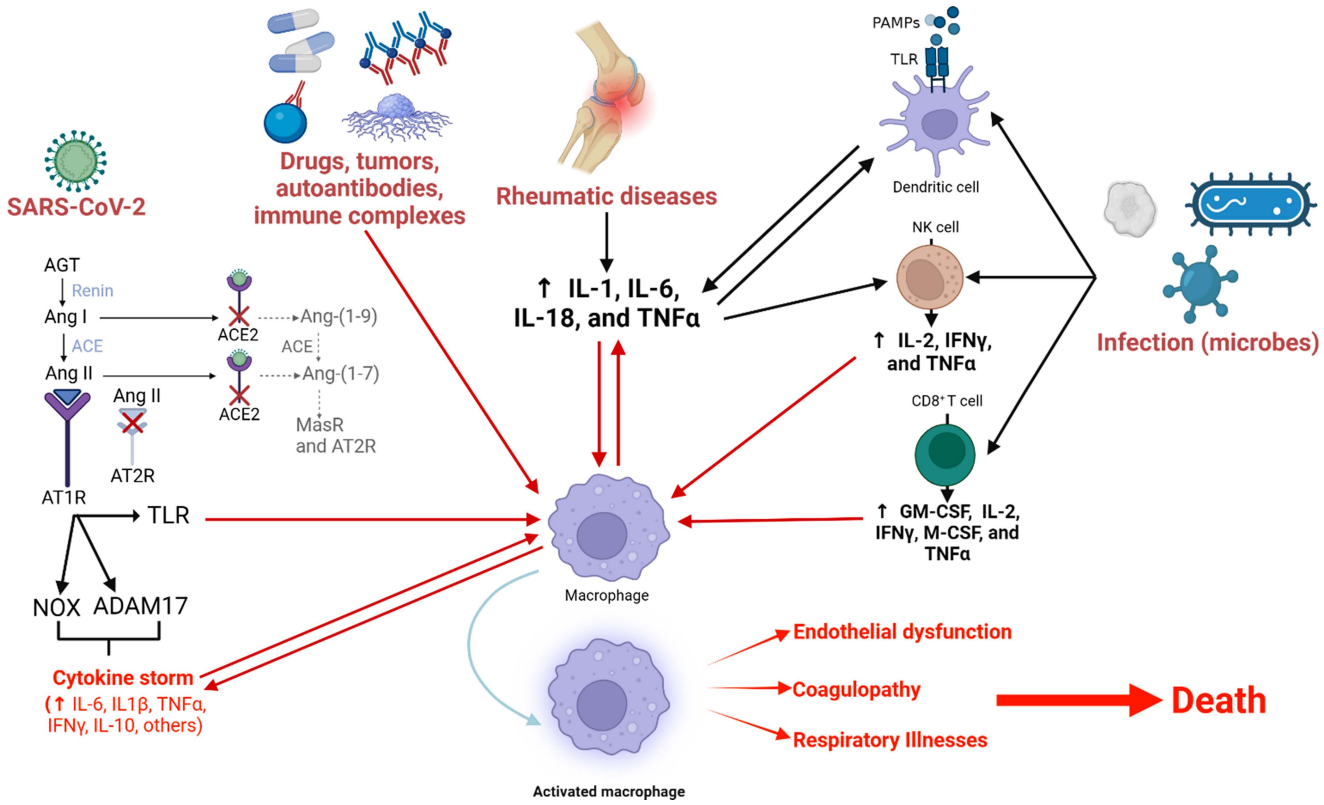

Fig. (1). Pathophysiological pathways contributing to Macrophage Activation Syndrome (MAS). MAS can develop due to various causes, including rheumatic diseases, drugs, tumors, antibodies, immune complexes, and infections. These triggers activate macrophages by stimulating cytokine production. Regarding SARS-CoV-2 infection, it can induce MAS through multiple mechanisms, including the activation of TLR, NOX, and ADAM-17 pathways. MAS can lead to several complications, such as endothelial dysfunction, coagulopathy, respiratory illnesses, and potentially contribute to death. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Following the COVID-19 pandemic that has affected the world in recent years and led to the application of various treatment procedures [16, 17], numerous cases of MAS syndrome have been documented in the literature. There has been an increase in MAS cases attributed to the SARS-CoV-2 virus and anti-SARS-CoV-2 vaccination, with several reported instances [13, 18, 19]. Indeed, the SARS-CoV-2 spike protein, whether from viruses or vaccine spike protein, can induce various issues and illnesses in humans, including MAS [20-35]. Following SARS-CoV-2 interaction with its angiotensin-converting enzyme 2 (ACE2) receptor, dysregulation of the renin–angiotensin system (RAS) occurs, resulting in elevated levels of Angiotensin II (Ang II). Ang II binds to the Ang II Type I Receptor (AT1R), triggering TLR activation and macrophage overproduction [12, 22], which can lead to MAS. Several other processes are also activated: (i) Ang II increases reactive oxygen species (ROS) production via the AT1R receptor by inducing NADPH oxidase (NOX), leading to mitochondrial dysfunction, DNA damage, and activation of the NF-κB pathway; (ii) Ang II stimulates ADAM17 through the p38/MAPK pathway, which cleaves membrane-bound forms of EGF and makes TNF-α generate their soluble forms to stimulate NF-κB further. This pathway contributes to COVID-19 pathogenesis and cytokine storm by promoting the expression of proinflammatory genes encoding IL-6, IL-8, and TNFα. Moreover, ADAM17 cleaves IL-6Rα to its soluble form (sIL-6Rα), which complexes with IL-6 to activate the gp130 receptor, triggering the JAK/STAT3 pathway and excess IL-6 production. These mechanisms can also precipitate the MAS induced by these inflammatory molecules. Following MAS, there is excessive secretion of inflammatory cytokines, resulting in a heightened inflammation state and lymphopenia (reduced $CD4^+$ and $CD8^+$ T cells). Reduced interferon production contributes to diminished NK cell activity, impairing viral control and delaying viral clearance. This immune imbalance leads to hyperactivated macrophages and neutrophils, causing tissue damage. In severe cases, endothelial dysfunction, ARDS, and coagulopathy lead to multiorgan failure, progressing to a severe state and potentially death (Fig. **1**) [12, 21, 22].

CONCLUSION

MAS is a very severe condition that can be fatal. Following infection with SARS-CoV-2 or vaccination, particularly with mRNA encoding the viral spike protein, many cases of MAS have been reported in published studies. We reiterate our suggestion regarding the importance of the impairment of the RAS in contributing to numerous non-genetic human diseases, including immunological syndromes [35]. Management MAS typically involves high-dose corticosteroids, which can occasionally lead to fatal outcomes. Alternative treatments such as cyclosporin A (CyA), TNFα inhibitors, and IL-1 blockers like anakinra have

shown varying degrees of success, with CyA being notably effective in severe or corticosteroid-resistant cases. Additionally, drugs that inhibit the RAS (such as ACE inhibitors, renin inhibitors, and AT1R antagonists) and blockers of the TLR4 receptor show promise in managing MAS [15, 35]. Given the severity of MAS and its potentially life-threatening complications, further studies are warranted on this syndrome, particularly regarding its diagnosis and management, especially in the context of SARS-CoV-2 and/or an anti-COVID-19 vaccine-induced pathogenesis.

AUTHORS' CONTRIBUTIONS

Z.F., L.T., Z.A.K.and J.M.S. contributed to the research design and implementation, as well as the data analysis and manuscript writing.

LIST OF ABBREVIATIONS

ADAM-17 = A Desintegrin and Metalloprotease Domain-containing Protein 17

ARDS = Acute Respiratory Distress Syndrome

EGF = Epidermal Growth Factor.

GAS = Gamma-activated Site

GM-CSF = Granulocyte-Macrophage Colony-Stimulating Factor

IFNGR = Interferon-Gamma Receptor

IL-1 = Interleukin 1

IL-18 = Interleukin 18

IL-6 = Interleukin 6

IL-6Rα = interleukin-6 receptor Alpha Subunit

JAK1 = Janus Kinase 1

JAK2 = Janus Kinase 2

M-CSF = Macrophage Colony-Stimulating Factor

NOX = Nitrogen Oxides

P38/MAPK = p38 Mitogen-activated Protein Kinase

STAT1 = Signal Transducer and Activator of Transcription 1

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Ravelli A, Minoia F, Davì S, *et al.* 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: A european league against rheumatism/american college of rheumatology/paediatric rheumatology international trials organisation collaborative initiative. Arthritis Rheumatol 2016; 68(3): 566-76.
http://dx.doi.org/10.1002/art.39332
PMID: 26314788

[2] Grom AA, Passo M. Macrophage activation syndrome in systemic juvenile rheumatoid arthritis. J Pediatr 1996; 129(5): 630-2.
http://dx.doi.org/10.1016/S0022-3476(96)70140-3
PMID: 8917224

[3] Schulert GS, Grom AA. Macrophage activation syndrome and cytokine-directed therapies. Best Pract Res Clin Rheumatol 2014; 28(2): 277-92.
http://dx.doi.org/10.1016/j.berh.2014.03.002 PMID: 24974063

[4] Sheu KM, Hoffmann A. Functional hallmarks of healthy macrophage responses: Their regulatory basis and disease relevance. Annu Rev Immunol 2022; 40(1): 295-321.
http://dx.doi.org/10.1146/annurev-immunol-101320-031555
PMID: 35471841

[5] Sreejit G, Fleetwood AJ, Murphy AJ, Nagareddy PR. Origins and diversity of macrophages in health and disease. Clin Transl Immunology 2020; 9(12): e1222.
http://dx.doi.org/10.1002/cti2.1222
PMID: 33363732

[6] Gerfaud-Valentin M, Sève P, Hot A, Broussolle C, Jamilloux Y. Pathophysiology, subtypes, and treatments of adult-onset Still's disease: An update. Rev Med Interne 2015; 36(5): 319-27.
http://dx.doi.org/10.1016/j.revmed.2014.10.365

[7] Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol 2008; 8(12): 958-69. http://dx.doi.org/10.1038/nri2448 PMID: 19029990
[8] Lerkvaleekul B, Vilaiyuk S. Macrophage activation syndrome: Early diagnosis is key. Open Access Rheumatol 2018; 10: 117-28. http://dx.doi.org/10.2147/OARRR.S151013 PMID: 30214327
[9] Stabile A, Bertoni B, Ansuini V, La Torraca I, Sallì A, Rigante D. The clinical spectrum and treatment options of macrophage activation syndrome in the pediatric age. Eur Rev Med Pharmacol Sci 2006; 10(2): 53-9. PMID: 16705949
[10] Crayne CB, Albeituni S, Nichols KE, Cron RQ. The immunology of macrophage activation syndrome. Front Immunol 2019; 10: 119. http://dx.doi.org/10.3389/fimmu.2019.00119 PMID: 30774631
[11] Sharma P, Shreshtha S, Kumar P, Sharma R, Mahapatra TK. A review on macrophage activation syndrome. J Pure Appl Microbiol 2019; 13(1): 183-91. http://dx.doi.org/10.22207/JPAM.13.1.19
[12] Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies. Annu Rev Med 2015; 66(1): 145-59. http://dx.doi.org/10.1146/annurev-med-061813-012806 PMID: 25386930
[13] Ravelli A, Davì S, Parodi A. Macrophage activation syndrome: Practice essentials, pathophysiology, etiology. 2024. Available from: https://emedicine.medscape.com/article/1380671-overview?form=login
[14] Minoia F, Davì S, Horne A, *et al.* Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: A multinational, multicenter study of 362 patients. Arthritis Rheumatol 2014; 66(11): 3160-9. http://dx.doi.org/10.1002/art.38802 PMID: 25077692
[15] Nierengarten MB. ACR/ARHP annual meeting: Macrophage activation syndrome. 2014. Available from: https://www.the-rheumatologist.org/article/2014-acrarhp-annual-meeting-macrophage-activation-syndrome/
[16] Cascella M, Rajnik M, Aleem A. Features, evaluation, and treatment of coronavirus (COVID-19). In: StatPearls. Treasure Island, FL: StatPearls Publishing 2024.
[17] Al-Jamal H, Idriss S, Roufayel R, Abi Khattar Z, Fajloun Z, Sabatier JM. Treating COVID-19 with medicinal plants: Is it even conceivable? A comprehensive review. Viruses 2024; 16(3): 320. http://dx.doi.org/10.3390/v16030320 PMID: 38543686
[18] Martínez-García JJ, López-Acosta JR, Arce-Cabrera D, *et al.* Case report: Multisystem inflammatory syndrome in children associated with COVID-19, macrophage activation syndrome, and incomplete Kawasaki disease. Front Pediatr 2023; 11: 1167828. http://dx.doi.org/10.3389/fped.2023.1167828 PMID: 37138560
[19] Abdelgabar A, Elsayed M. A case of delayed COVID-19-related macrophage activation syndrome. J Med Cases 2022; 13(5): 207-11. http://dx.doi.org/10.14740/jmc3903 PMID: 35655624
[20] Annweiler C, Cao Z, Wu Y, *et al.* Counter-regulatory 'renin-angiotensin' system-based candidate drugs to treat COVID-19 diseases in sars-cov-2-infected patients. Infect Disord Drug Targets 2020; 20(4): 407-8. http://dx.doi.org/10.2174/22123989MTA2cNzIlw PMID: 32418532
[21] El-Arif G, Farhat A, Khazaal S, *et al.* The renin-angiotensin system: A key role in SARS-COV-2-induced COVID-19. Molecules 2021; 26(22): 6945. http://dx.doi.org/10.3390/molecules26226945 PMID: 34834033
[22] El-Arif G, Khazaal S, Farhat A, *et al.* Angiotensin II type I receptor (AT1R): The gate towards COVID-19-associated diseases. Molecules 2022; 27(7): 2048. http://dx.doi.org/10.3390/molecules27072048 PMID: 35408447
[23] Khazaal S, Harb J, Rima M, *et al.* The pathophysiology of long COVID throughout the renin-angiotensin system. Molecules 2022; 27(9): 2903. http://dx.doi.org/10.3390/molecules27092903 PMID: 35566253
[24] Sabatier J-M, Fajloun Z, Legros C. COVID-19 and ehlers-danlos syndrome: The dangers of the spike protein of SARS-CoV-2. Infect Disord Drug Targets 2023; 23(3): e040123212375. http://dx.doi.org/10.2174/1871526523666230104145108 PMID: 36600622
[25] Fajloun Z, Abi Khattar Z, Kovacic H, Legros C, Sabatier JM. Why do athletes develop very severe or fatal forms of covid after intense exercise following SARS-CoV-2 infection or Anti-COVID vaccination? Infect Disord Drug Targets 2023; 23(4): e110123212563. http://dx.doi.org/10.2174/1871526523666230111104355 PMID: 36631923
[26] Fajloun Z, Abi Khattar Z, Kovacic H, Legros C, Sabatier JM. SIBO: The trail of a "New" human pathology associated with multiple severe and disabling COVID-19 and long covid symptoms or induced by the anti-COVID-19 vaccine. Infect Disord Drug Targets 2023; 23(4): e100223213593. http://dx.doi.org/10.2174/1871526523666230210162334 PMID: 36762752
[27] Fajloun Z, Abi Khattar Z, Kovacic H, Legros C, Sabatier JM. Anti-COVID-19 vaccination, COVID-19, and female contraception: The exacerbated risks (Thromboembolism) of the estrogen-progestin pill. Infect Disord Drug Targets 2023; 23(4): e240223214000. http://dx.doi.org/10.2174/1871526523666230224094439 PMID: 36823996
[28] Fajloun Z, Abi Khattar Z, Kovacic H, Legros C, Sabatier JM. Understanding and relieving of neuropathic disorders in the long COVID. Infect Disord Drug Targets 2023; 23(4): e270223214061. http://dx.doi.org/10.2174/1871526523666230227113205 PMID: 36843369
[29] Fajloun Z, Abi Khattar Z, Kovacic H, Sabatier JM. COVID-19 and anti-COVID-19 vaccination: Potential damages to the thyroid gland. Infect Disord Drug Targets 2023; 23(6): e090523216698. http://dx.doi.org/10.2174/1871526523666230509112038 PMID: 37165584
[30] Fajloun Z, Wu Y, Cao Z, Kovacic H, Sabatier JM. COVID-19 and alzheimer's disease: The link finally established. Infect Disord Drug Targets 2023; 23(7): 14-6. PMID: 37254552
[31] Fajloun Z, Wu Y, Cao Z, Kovacic H, Sabatier JM. COVID-19 and parkinson's disease: The link also established! Infect Disord Drug Targets 2023. PMID: 37340743

[32] Fajloun Z, Khattar ZA, Sabatier JM. The intriguing connection between cholestasis and the renin-angiotensin system dysregulation induced by SARS-CoV-2 and/or the vaccinal spike protein. Infect Disord Drug Targets 2024; 24(7): e080324227802.
http://dx.doi.org/10.2174/0118715265304515240220105152 PMID: 38465438

[33] Tajer L, Paillart JC, Dib H, Sabatier JM, Fajloun Z, Abi Khattar Z. Molecular mechanisms of bacterial resistance to antimicrobial peptides in the modern era: An updated review. Microorganisms 2024; 12(7): 1259.
http://dx.doi.org/10.3390/microorganisms12071259

[34] Fajloun Z, Abi Khattar Z, Sabatier JM. SARS-CoV-2 or vaccinal spike protein can induce mast cell activation syndrome (MCAS). Infect Disord Drug Targets 2024; 24: 1-3.
PMID: 38693735

[35] Fajloun Z, Sabatier JM. The unsuspected role of the renin-angiotensin system (RAS): Could its dysregulation be at the root of all non-genetic human diseases? Infect Disord Drug Targets 2024; 24(1): e140923221085.
http://dx.doi.org/10.2174/1871526524666230914114524 PMID: 37711109